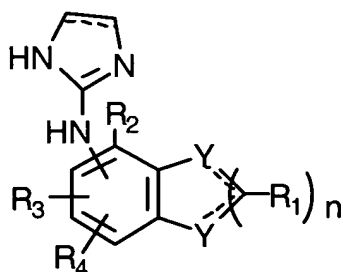


STATUS OF CLAIMS

APPENDIX
Claims on Appeal

1) (Currently amended) A topical ophthalmic composition useful for ~~controlling elevated intraocular pressure associated with glaucoma and ocular hypertension while~~ providing neuroprotection to the ocular neural tissue~~nerve~~s, comprising a combination of a therapeutically effective amount of a prostaglandin and a therapeutically effective amount of an alpha adrenergic agent of formula (I)



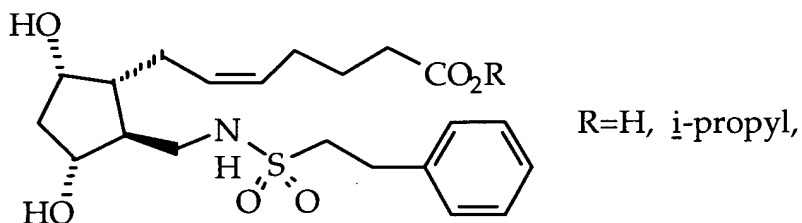
formula (I)

wherein each Y is independently selected from the group consisting of N, N-CH₃, O, S and C-R₁; R₁ is hydrogen, lower alkyl or oxo; R₂, R₃ and R₄ are independently selected from the group consisting of hydrogen, halogen, lower alkyl and lower alkenyl; n is an integer from 1 to 3; and a broken line beside a solid line indicates a single or double bond, provided that two double bonds are not on the same carbon in the case when n=1, and their pharmaceutically acceptable salts and esters as appropriate, wherein such therapeutically effective amounts are sufficient to provide neuroprotection to such tissue. ~~said composition lowers intraocular pressure and provides neuroprotection.~~

2) (Original) The composition of claim 1 wherein the prostaglandin is selected from the group consisting of PGF_{2α}, PGE₂, PGE₁, prostacyclin, 15(S)-methyl-PGF_{2α}, 16,16-dimethyl-PGF_{2α}, 15(S)-methyl-PGE_{2α}, 16,16-dimethyl-PGE₂, 17,18,19,20-tetranor-16-phenoxy-PGE₂, 17,18, 19,20-tetranor-16-phenoxy-PGF_{2α}, 18,19,20-trinor-17-phenyl-PGE₂, 18,19,20-trinor-17-phenyl-PGF_{2α}, the free acid and lower alkyl esters of PGF_{2α}, wherein the omega chain has been replaced with phenylethylsulfonamidomethyl-, trimoprostil, RS-84-135, rioprostil, S-1033 (15-deshydroxy PGF_{2α} sodium salt), S-747260, nocloprost, CS-412, YPG-209, K-10134, cloprostenol, fluprostenol, luporstiol, etiproston, tiaprost, SQ 27986, ZK 138519, 13,14-dihydro-ZK 138519, ZK 118182, 13,14-dihydro-ZK 118182, ZK 110841, 13,14-dihydro-ZK 110841, PhXA41 (latanoprost), RO-221327, HR-466, HR-601, ONO-1206, UFO-21, 11-deoxy-PGE₂, 11-deoxy-PGF_{2α}, 11-deoxy-16,16-dimethyl-PGE₂, 11-deoxy-15(S)-

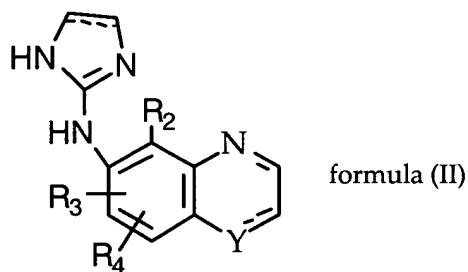
methyl-PGE₂, 11-deoxy-15(S)-methyl-PGF_{2α}, misoprostol, enisoprost, MDL-646, CL-115,574, CL-115,347, TR-4161, TR-4752, TR-4367, CP-27987, sulprostone, gemeprost, alfaprostol, delprostenate, prostalene, fenprostalene, CL-116,069, ONO-995 and RO-229648, and their pharmaceutically acceptable esters and salts, as appropriate.

3) (Original) The composition of claim 2 wherein the prostaglandin is selected from the group consisting of PGF_{2α}-11-pivalyl ester, the 1-amido-15-methyl ether of PGF_{2α}, 1-ethylamido-18,19,20-trinor-17-phenyl-PGF_{2α}, PGF_{2α}-1-ethyl ester, PGF_{2α}-1-isopropyl ester, the acid and isopropyl ester derivatives of PGF_{2α} wherein the omega chain has been replaced with phenylethylsulfonamidomethyl-, as represented by the structure below:



RO-229648, SQ 27986, ZK 138519, 13,14-dihydro-ZK 138519, ZK 110841, 13,14-dihydro-ZK 110841, PhXA41, and 18,19,20-trinor-17-phenyl-PGF_{2α}-1-methyl ester.

4) (Original) The composition of claim 1 wherein the alpha adrenergic agent is selected from the group consisting of formula (II) wherein Y is N or O, R₂ is bromine or methyl and all other variables are defined as in claim 1.

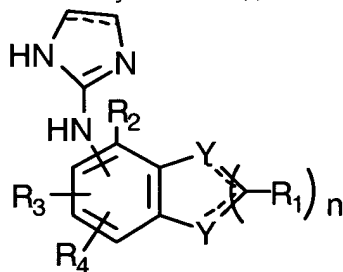


5) (Original) The composition of claim 3 wherein the alpha adrenergic agent is brimonidine (5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine).

6) (Original) The composition of claim 4 wherein the alpha adrenergic agent is brimonidine (5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine).

7-13) (Cancelled).

14) (Currently amended) An article of manufacture comprising packaging material and a pharmaceutical combination comprising at least one alpha adrenergic agent and at least one prostaglandin and their pharmaceutically acceptable salts and esters as appropriate, wherein the combination is ~~pharmaceutical agents are effective in controlling elevated intraocular pressure associated with glaucoma and ocular hypertension and~~ providing neuroprotection, and wherein the packaging material comprises a label which indicates that said combination can be used for neuroprotection ~~control of elevated intraocular pressure or in treating glaucoma~~, and wherein said alpha adrenergic agent is represented by formula (I)



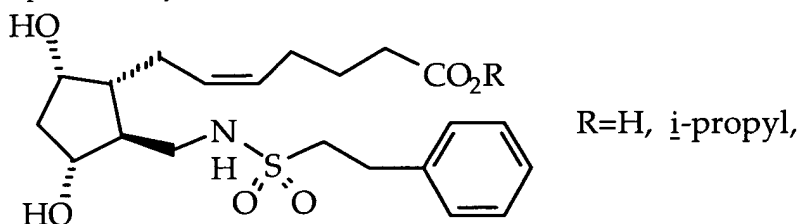
formula (I)

wherein each Y is independently selected from the group consisting of N, N-CH₃, O, S and C-R₁; R₁ is hydrogen, lower alkyl or oxo; R₂, R₃ and R₄ are independently selected from the group consisting of hydrogen, halogen, lower alkyl and lower alkenyl; n is an integer from 1 to 3; and a broken line beside a solid line indicates a single or double bond, provided that two double bonds are not on the same carbon in the case when n=1.

15) (Original) The article of claim 14 wherein the prostaglandin is selected from the group consisting of PGF₂α, PGE₂, PGE₁, prostacyclin, 15(S)-methyl-PGF₂α, 16,16-dimethyl-PGF₂α, 15(S)-methyl-PGE₂α, 16,16-dimethyl-PGE₂, 17,18,19,20-tetranor-16-phenoxy-PGE₂, 17,18, 19,20-tetranor-16-phenoxy-PGF₂α, 18,19,20-trinor-17-phenyl-PGE₂, 18,19,20-trinor-17-phenyl-PGF₂α, the free acid and lower alkyl esters of PGF₂α, wherein the omega chain has been replaced with phenylethylsulfonamidomethyl-, trimoprostil, RS-84-135, rioprostil, S-1033 (15-deshydroxy PGF₂α, sodium salt), S-747260, nocloprost, CS-412, YPG-209, K-10134, cloprostenol, fluprostenol, luporstiol, etiproston, tiaproston, SQ 27986, ZK 138519, 13,14-dihydro-ZK 138519, ZK 118182, 13,14-dihydro-ZK 118182, ZK 110841, 13,14-dihydro-ZK 110841, PhXA41 (latanoprost), RO-221327, HR-466, HR-601, ONO-1206, UFO-21, 11-deoxy-PGE₂, 11-deoxy-PGF₂α, 11-deoxy-16,16-dimethyl-PGE₂, 11-deoxy-15(S)-methyl-PGE₂, 11-deoxy-15(S)-methyl-

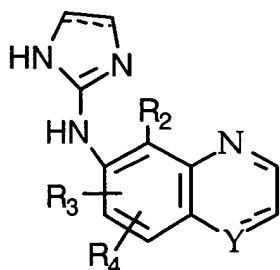
PGF2 α , misoprostol, enisoprost, MDL-646, CL-115,574, CL-115,347, TR-4161, TR-4752, TR-4367, CP-27987, sulprostone, gemeprost, alfaprostol, delprostenate, prostalene, fenprostalene, CL-116,069, ONO-995 and RO-229648, and their pharmaceutically acceptable esters and salts, as appropriate.

16) (Original) The article of claim 15 wherein the prostaglandin is selected from the group consisting of PGF2 α -11-pivalyl ester, the 1-amido-15-methyl ether of PGF2 α , 1-ethylamido-18,19,20-trinor-17-phenyl-PGF2 α , PGF2 α -1-ethyl ester, PGF2 α -1-isopropyl ester, the acid and isopropyl ester derivatives of PGF2 α wherein the omega chain has been replaced with phenylethylsulfonamidomethyl-, as represented by the structure below:



RO-229648, SQ 27986, ZK 138519, 13,14-dihydro-ZK 138519, ZK 110841, 13,14-dihydro-ZK 110841, PhXA41, and 18,19,20-trinor-17-phenyl-PGF2 α -1-methyl ester.

17) (Original) The article of claim 14 wherein the alpha adrenergic agent is selected from the group consisting of formula (II) wherein Y is N or O, R₂ is bromine or methyl and all other variables are defined as in claim 14



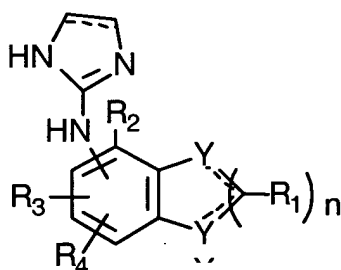
formula (II)

18) (Original) The article of claim 16 wherein the alpha adrenergic agent is brimonidine (5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine).

19) (Original) The article of claim 17 wherein the alpha adrenergic agent is brimonidine (5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine).

20) (Original) The article of claim 14 wherein the prostaglandin is the 11-pivalyl ester of PGF2 α and the alpha adrenergic agent is brimonidine.

21) (Original) A method of preventing degeneration of the optic nerve and providing protection of the retinal ganglion cells of a mammal, comprising administering to the mammal a therapeutically effective amount of a prostaglandin and a therapeutically effective amount of an alpha adrenergic agent of formula (I)



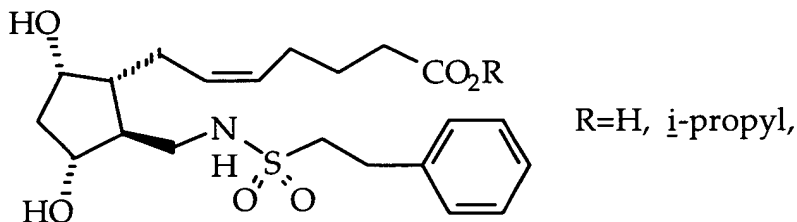
formula (I)

wherein each Y is independently selected from the group consisting of N, N-CH₃, O, S and C-R₁; R₁ is hydrogen, lower alkyl or oxo; R₂, R₃ and R₄ are independently selected from the group consisting of hydrogen, halogen, lower alkyl and lower alkenyl; n is an integer from 1 to 3; and a broken line beside a solid line indicates either a single or a double bond, provided that two double bonds are not on the same carbon in the case when n=1, and their pharmaceutically acceptable salts and esters as appropriate.

22. (Original) The method of claim 21 wherein the prostaglandin is selected from the group consisting of PGF2 α , PGE2, PGE1, prostacyclin, 15(S)-methyl-PGF2 α , 16,16-dimethyl-PGF2 α , 15(S)-methyl-PGE2a, 16,16-dimethyl-PGE2, 17,18,19,20-tetranor-16-phenoxy-PGE2, 17,18, 19,20-tetranor-16-phenoxy-PGF2 α , 18,19,20-trinor-17-phenyl-PGE2, 18,19,20-trinor-17-phenyl-PGF2 α , the free acid and lower alkyl esters of PGF2 α , wherein the omega chain has been replaced with phenylethylsulfonamidomethyl-, trimoprostil, RS-84-135, rioprostil, S-1033 (15-deshydroxy PGF2 α , sodium salt), S-747260, nocloprost, CS-412, YPG-209, K-10134, cloprostenol, fluprostenol, luporstiol, etiproston, tiaprost, SQ 27986, ZK 138519, 13,14-dihydro-ZK 138519, ZK 118182, 13,14-dihydro-ZK 118182, ZK 110841, 13,14-dihydro-ZK 110841, PhXA41 (latanoprost), RO-221327, HR-466, HR-601, ONO-1206, UFO-21, 11-deoxy-PGE2, 11-deoxy-PGF2 α , 11-deoxy-16,16-dimethyl-PGE2, 11-deoxy-15(S)-methyl-PGE2, 11-deoxy-15(S)-methyl-PGF2 α , misoprostol, enisoprost, MDL-646, CL-115,574, CL-115,347, TR-4161, TR-4752, TR-4367, CP-27987, sulprostone, gemeprost, alfaprostol, delprostenate,

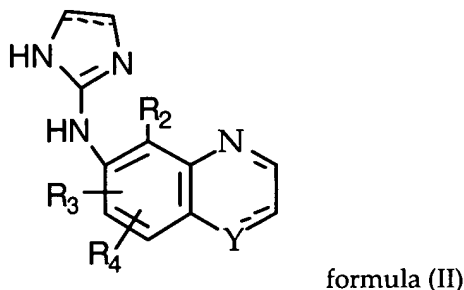
prostaglandin, fenprostalene, CL-116,069, ONO-995 and RO-229648, and their pharmaceutically acceptable esters and salts, as appropriate.

23) (Original) The method of claim 22 wherein the prostaglandin is selected from the group consisting of PGF2 α -11-pivalyl ester, the 1-amido-15-methyl ether of PGF2 α , 1-ethylamido-18,19,20-trinor-17-phenyl-PGF2 α , PGF2 α -1-ethyl ester, PGF2 α -1-isopropyl ester, the acid and isopropyl ester derivatives of PGF2 α wherein the omega chain has been replaced with phenylethylsulfonamidomethyl-, as represented by the structure below:



RO-229648, SQ 27986, ZK 138519, 13,14-dihydro-ZK 138519, ZK 110841, 13,14-dihydro-ZK 110841, PhXA41, and 18,19,20-trinor-17-phenyl-PGF2 α -1-methyl ester.

24) (Original) The method of claim 21 wherein the alpha adrenergic agent is selected from the group consisting of formula (II) wherein Y is N or O, R2 is bromine or methyl and all other variables are defined as in claim 14



25) (Original) The method of claim 23 wherein the alpha adrenergic agent is brimonidine (5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine).

26) (Canceled).

27) (Original) The article of claim 21 wherein the prostaglandin is the 11-pivalyl ester of PGF2 α and the alpha adrenergic agent is brimonidine.

Serial No. 09/903,954
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PATENT

Respectfully submitted,

Dated: April 5, 2005

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